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EXAMINER
EISENSCHENK, J

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DATE MAILED: 05/27/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/23/94 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-14 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 15-31 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-14 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

STATUS OF THE CLAIMS

PENDING: 1-27, 31
CANCELLED: 28-30

15. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views). Applicant is reminded to amend the specification to reflect any corrections made to the drawings. The Office has made minor corrections to the CRF filed 7/29/93. These corrections involve the deletion of all hard page break codes found in the CRF submission.

16. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

17. Claims 1-27 and 31 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the antibodies produced by the claimed methodology. Applicant alleges the antibodies produced by the claimed methodology are useful in therapeutic regimens. No evidence has been provided to support such allegations of utility.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

It is well known in the art that correlation between in vitro assays and in vivo animal studies to in vivo human efficacy is a major barrier. Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing

with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3). Harris et al. also teach that humanised antibodies show promise for human therapy, however the data was derived from immunosupressed individuals not representative of a normal population (paragraph bridging pages 42-43). Thus, the efficacy of using humanized antibodies for immunotherapy is still considered unpredictable by those of ordinary skill in the art. Applicant's attention is also drawn to Osband et al. where the difficulties between clinical immunotherapy and investigational study of antibody based cancer therapies are set forth. Paragraph 3 of Osband teaches that there exists a lack of useful animal models that can be applied to immunotherapy. Osband et al. further teach that animal models are not generally predictive of therapeutic efficacy in humans as relates to immunotherapy regimens. Furthermore, it is taught that immunotherapy regimens intended for humans will have to be developed in humans (last sentence, paragraph 3). Hird et al. teach (page 185, paragraph 2) the biodistribution of murine antibodies in vivo when compared between humans and mice to be vastly different and that trends in small animal studies do not necessarily correlate to efficacious therapy in humans. Furthermore, Applicant has produced the recombinant antibodies in COS cells. These cells are of non-human primate origin. The art recognizes the importance of glycosylation patterns in the recognition of self versus non-self and the use of cell lines of non-human origin will result in non-human glycosylation patterns and may give rise to an immunogenic response to the recombinantly produced proteins upon their injection into humans.

Therefore it does not appear that the asserted utility of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p).

The provisions of 35 U.S.C. § 101 require that claimed subject matter must be useful to be eligible for patentability. Case law has established that utility may not be based on mere assertion, but rather must be definite and in currently available form. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). Initially, the burden is always on the Examiner to establish some reason to doubt the asserted utility of the claimed invention. If the asserted utility is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art at the time the application is filed, then the burden is on the Examiner to provide reasons or evidentiary proof to substantiate a rejection based on lack of utility under 35 U.S.C. § 101. In the instance wherein the statements would be deemed unlikely

to be correct by one skilled in the art in view of the contemporary knowledge in the art, the burden of adequate proof shifts to the applicant. In order to provide proof of utility with regard to monoclonal antibodies (drugs) and their uses, either clinical, in vivo, or in vitro data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed utility is sufficiently established. See In re Irons, 340 F.2d 924, 144 USPQ 351 (CCPA 1965); Ex parte Krepelka, 231 USPQ 746 PTO Bd. Pat. App. & Inter. 1986); and Ex parte Chwang, 231 USPQ 751 (PTO Bd. Pat. App & Inter. 1986). When the utility is directed to humans, the data must generally be clinical. In order to accept animal data, there must exist an art recognized animal model for testing purposes. See In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962).

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) Applicants have not adequately disclosed how to use the recombinantly produced primate derived antibody molecules as therapeutic agents for the treatment of disease in humans. There is insufficient written description of the invention with respect to the in vivo operability of the claimed invention to use applicant's invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 17).

20. Claims 1-27 and 31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see paragraph 19).

21. Claims 1-27 and 31 are rejected under 35 U.S.C. § 112, first

paragraph, as the disclosure is not enabling for the use of the claimed invention as a diagnostic aid or as a therapeutic agent. Applicant has supplied no teaching or disclosure in the application which would enable one of ordinary skill to use the antibodies produced by the claimed methods in either therapeutic or diagnostic regimens.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1-2, 4-5, 7-10, 12-16, and 26-27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gilles et al. Gilles et al. teach methods for the production of human (primate) antibodies (specifically anti-tetanus antibodies) from cDNA libraries, as well as transfected cell lines, transfecting vectors, and a recombinant human (primate antibody that would be useful for the treatment of tetanus poisoning (see Materials and Methods).

24. Claim 31 is rejected under 35 U.S.C. § 102(b) as being anticipated by Harris et al. (EP 314161) Harris et al. teach methods for making therapeutic compositions comprising the mixing of a recombinant human (primate) antibody in a physiologically acceptable diluent (see page 41, paragraph 4). PBS is an art recognized physiologically acceptable carrier.

25. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies

as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

26. Claims 3, 6 and 17-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Gillies et al. in view of Foung et al. (WO 87/01131) and Ehrlich et al. The claims are drawn to methods for the production of recombinant chimpanzee or old world monkey antibodies specific for hepatitis virions. Gillies et al. teach methods for the production of recombinant human antibodies from cDNA libraries. Gillies et al. do not anticipate the claimed invention because methods for the production of recombinant non-human primate antibodies is not taught. Foung et al. teach the production of chimpanzee monoclonal antibodies specific for non-A, non-B hepatitis virus. Foung et al. teach that desirable alternative sources of B-cells are non-human primates because antibodies from phylogenetically related primates would not be expected to engender an immunize response upon administration to humans and these primates may be immunized with antigens which cannot be administered to humans (see paragraph bridging pages 4-5). Those skilled in the art would have recognized that such antigens include HIV virus, hepatitis A or B, or any other pathogen with which one could use in the immunization of the chimpanzee. The teachings of Ehrlich et al. indicate that human antibodies are non-immunogenic in Rhesus monkeys (page 23, paragraph 1) and that the chimpanzee immunoglobulin genes are extremely similar in nucleic acid sequence and amino acid sequence (page 26, paragraph 1). Ehrlich et al. further teach that the immunogenicity of chimpanzees is expected to be low or non-existent in humans. Coupling these teachings, one of ordinary skill in the art would have expected that the use of rhesus (or related) monkey or chimpanzee antibodies in humans would not lead to significant immunological responses in humans. Accordingly, one of ordinary skill would expect that the nucleic acids encoding such antibodies would allow for the recombinant expression of antibodies derived from these primates that would have similar if not identical properties (i.e. low immunogenicity). The nucleic acids encoding these antibodies could have been isolated from these primate B-cells following the teachings of Gillies et al. in view of the high degree of sequence homology between primate immunoglobulin genes and those of human origin (see Ehrlich et al., last 2 paragraphs).

One of ordinary skill in the art at the time the invention was made would have been motivated to design a method for

the production of non-human primate antibodies by recombinant methods because such antibodies would have potential therapeutic or diagnostic value. The combined teachings of Gillies et al., Foung et al., and Ehrlich et al. would allow for the isolation of primate nucleic acid which encoded immunoglobulin molecules potentially useful for therapy or diagnostic use. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

27. Claim 11 is rejected under 35 U.S.C. § 103 as being unpatentable over Gillies et al. in view of Larrick et al. The claim is drawn to a method for the production of recombinant antibodies using micro-preps of RNA. Gillies et al. teach methods for the production of recombinant human antibodies from cDNA libraries. Gillies et al. do not anticipate the claimed invention because methods for the production of recombinant antibodies from micro-preparations of RNA is not taught. Larrick et al. teach that the variable regions of an antibody molecule produced by a single B-cell can be isolated (see page 93, paragraph 3). The combined techniques of Larrick et al. and Gillies et al. would allow for the isolation of an immunoglobulin gene from even one B-cell and its subsequent recombinant expression, let alone 1000 B-cells of the same antigenic specificity.

One of ordinary skill in the art at the time the invention was made would have been motivated to design a method for the production antibodies by recombinant methods from as few as 1000 B-cells because such a method would allow for the rescue of antibody genes from B-cells of poor viability. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

28. Claim 25 is rejected under 35 U.S.C. § 103 as being unpatentable over Gillies et al. in view of Foung et al. (WO 87/01131), Ehrlich et al. and Harris et al. (EP 314161). Claim 25 is drawn to a pharmaceutical composition comprising recombinant non-human primate antibodies in pharmaceutical carriers. The teachings of Gillies et al., Ehrlich et al., and Foung et al. have been discussed supra. These

references do not teach the claimed invention because the combined references do not teach pharmaceutical compositions of the recombinant non-human primate antibodies. Harris et al. teaches (page 3, lines 55-58) the combination of recombinant human antibodies in pharmaceutically acceptable carriers because the antibodies may then be used in therapeutic or diagnostic regimens. Pharmaceutical compositions comprising the recombinant non-human primate antibodies made according to the methods of Gillies et al., Foung et al., and Ehrlich et al. would have been prima facie obvious to one of ordinary skill because such antibodies would then be in pharmaceutically acceptable excipients suitable for human use.

One of ordinary skill in the art at the time the invention was made would have been motivated to suspend recombinant non-human primate antibodies in pharmaceutical excipients because such antibodies would have potential therapeutic or diagnostic utility and be suitable for injection. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

29. No claim is allowed.

30. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Christopher Eisenschenk whose telephone number is (703) 308-0452. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

F. Christopher Eisenschenk, Ph.D.
September 21, 1993

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
9/22/93